PROCESS VALIDATION OF PERAMPANEL TABLET ANTI CONVULSANT DRUG

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Submitted By

Sanneboyina Nagarjuna

(Reg No:261211162)

Under the guidance of

Mr.M.Pitchaipillai, M.Pharm.,

DEPARTMENT OF PHARMACEUTICS

EDAYATHANGUDY.G.S PILLAY COLLEGE OF PHARMACY

NAGAPATTINAM-611002

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Mr.M.Pitchaipillai, M.Pharm.,

Department of Pharmaceutics,

Edayathangudy.G.S.Pillay College of Pharmacy,

Nagapattinam – 611 002.

CERTIFICATE

This is to certify that the dissertation entitled **"PROCESS VALIDATION OF PERAMPANEL TABLET ANTI CONVULSANT DRUG"** submitted by **SANNEBOYINA NAGARJUNA** (Reg No:261211162) in partial fulfillment for the award of degree of Master of Pharmacy to the Tamilnadu Dr. M.G.R Medical University, Chennai is an independent bonafide work of the candidate carried out under my guidance in the Department of Pharmaceutics, Edayathangudy.G.S.Pillay College of Pharmacy during the academic year 2013-2014.

Place: Nagapattinam **Mr.M.Pitchaipillai, M.Pharm.,**

Date:

Prof.Dr.D.Babu Ananth,M.Pharm., Ph.D.,

Principal,

Edayathangudy.G.S.Pillay College of Pharmacy,

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Place: Nagapattinam **Prof.Dr.D.BabuAnanth,M.Pharm., Ph.D.,**

Date:

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INTRODUCTION

Validation is a subject that has grown in importance within the global healthcare industry over the past 25 years. During that time period, it has perhaps resulted in more changes in practices and methods.

One of the major concerns with any design whether it be for a facility , a piece of equipment or a production process- is how its validation will be accomplished.

Validation programs must be established to facilitate the accomplishment of that very goal. A clear line of communication must be established to ensure that the operational objectives as implemented in the design can meet the validation requirements for that design.[1]

HISTORICAL BACKGROUND:

The idea of process validation is not new and is common in many different fields of life; one can find the need for process validation in almost any kind of process. Sharp interpreted pharmaceutical process validation simply as a step in developing the maintenance of the quality of manufactured medicines. Process validation has been included in the first interpretations of good manufacturing practice (GMP) to ensure that medicines are safe and have the identity and strength they are supposed to have.

US regulations. Bernard T. Loftus, a former director of FDA, previously described how the principles of process validation evolved in the US from the first current good manufacturing practice (cGMP) in 1963 to the first Guideline on General Principles of Process Validation in 1987. Prior to 1963, the only way for FDA to prove that a

process had not done what it was designed to do was to take samples from the final product, analyse them and show deviations from the specification.

From 1963, the law stated that a pharmaceutical manufacturer had to follow cGMP regulations whilst FDA received authorization to inspect manufacturing facilities. This was a direct consequence of a series of accidents in which people were injured and even killed.

These incidents led to the evaluation of manufacturing processes, but it still took a long time before the authorities could point out clear and serious production faults and demand better procedures and processes.

Things began to change during the late 1960s and early 1970s when new types of incidents, such as poorly mixed, highly potent tablets and insufficient sterilization procedures for large volume parenterals caused serious patient disorders. Many speeches pointing out the need for process validation were made by US authorities and the expression "validated manufacturing process" was finally defined in the Drug Process Inspections Compliance Program in 1978. The more precise definition and adjustment of the concept for process validation was published in the Guideline on General Principles of Process Validation in 1987 and, since then, exhaustive process inspections have been routinely performed by FDA. It took a long time before process validation was directly named in US cGMP regulations.[2]

On march 29, 1983 draft on guidelines entitled “Guidelines on General principles of process validation” was made available & the same was finalized in may 1987 [3]

The finalized definition was as follows “A documented programme, which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications & quality attributes. [3,4]

New definition of process validation as "the collection and evaluation of data, from the process design stage through production, which establishes scientific evidence that a process is capable of consistently delivering quality products". Thus, process validation is now split up into 3 stages shown in figure 1:

- Stage 1 "Process Design" (The commercial process is based on experiences gained from development and scale-up)
- Stage 2 "Process Qualification" (During this stage, the reproducible, commercial scale is confirmed on the basis of process design)
- Stage 3 "Continued Process Verification" (This stage is meant to show that the process is in a state of control during routine production)

The text states expressly that in practice these 3 stages might overlap. With emphasis, it urges manufacturers to prove with a high degree of assurance that the product can be manufactured according to the quality attributes before a batch is placed on the market. For this purpose, data from laboratory-, scale-up and industrial scale are meant to be

used. The data are explicitly meant to cover conditions involving a great risk of process variation.

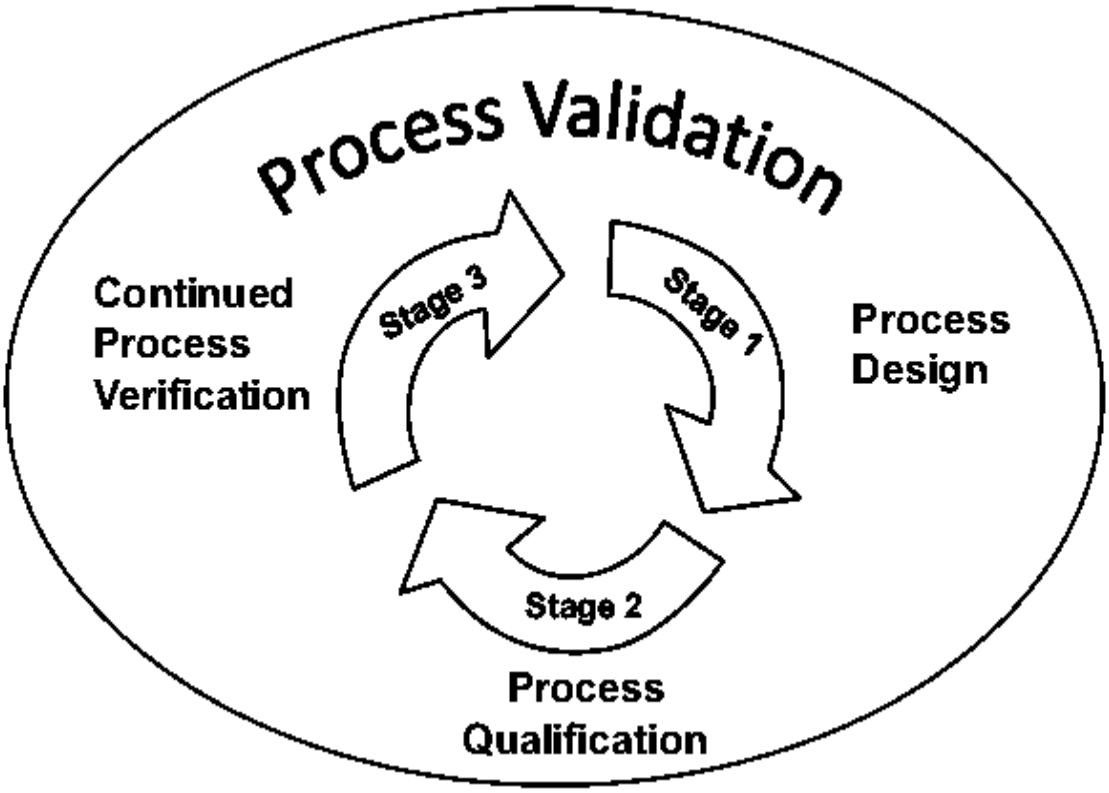


Figure 1: Three stage model of process validation according to FDA Guidance for Industry – Process Validation

FDA Guidance for Industry – Process Validation: General Principles and Practices describes process validation as an integral part of a product's entire life cycle. For this purpose the familiar concepts of the current ICH Guidelines Q8 (R2) Pharmaceutical Development, Q9 Quality Risk Management and Q10 Pharmaceutical Quality System are embraced and applied to the topic of process validation:

- Extension of validation activities to the entire life cycle instead of selective measures (e.g. "three validation batches")
- Profound understanding of the processes and risk-based approaches as a basis for the validation activities instead of formal processing of long checklists.
- Continuous process enhancement and innovation instead of predefined processes and parameters.
- Importance of scientific principles (Sound Science) and of knowledge transfer from development.
- Demand for support by the senior management.[5]

Validation is an integral part of the quality assurance and its simple meaning is 'action of proving'. It involves controlling the critical steps of a system, which results in output of repeatable attributes validation itself does not improve the process but confirms consistent output. [6]

TYPES OF VALIDATION:

Following are the different types of validation.

* Process validation
* Analytical method validation
* Cleaning validation
* Water system validation
* Computer system validation
* Equipment qualification
* Facility qualification

Qualification is the subset of validation. Qualification and validation only appear to be the beginning of a continues development process in the quality assurance of the pharmaceutical industry. Equipment or equipment systems are qualified & processes are validated.

WHY VALIDATION:

The prime objective of the pharmaceutical plant, whether in production or in quality control is to manufacture consistently products of the requisite quality at the lowest possible cost.

According to FDA, assurance of product quality is derived from careful and systematic attention to a number of important factors, including selection of quality components and materials, adequate product and process design and control of the process through in-process and end-product testing.

Thus, it is through careful design (qualification) and validation of both the process and its control systems that a high degree of confidence can be established that all the individual manufacturing units of a given batch or succession of batches that meet specifications will be acceptable.

GMPs and validation, two concepts that cannot be separated are essentially to quality assurance. Frequently, the validation of a process will lead to quality improvement, in addition to better quality consistency.

The reasons why pharmaceutical industry is concerned that their process performs consistently as expected that is, they are validated. [6,12]

Assurance of quality:

It is important for the well understanding that, the process is in a state of control and to get confidence in the quality of the product manufactured.

Cost reduction:

Experience and common sense indicates that a validated process is a more efficient process and a process that possesses less re-works, rejects, wastages and so on.

Regulatory requirement:

Validation is considered to be an integral part of GMPs. Worldwide compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products.

Process optimization:

The optimization of a process for maximum efficiency, while maintaining quality standards is a consequence of validation. The optimization of the facility, equipment, systems and processes results in a product that meets quality requirements at the lowest cost.

PRINCIPLES OF VALIDATION:

The basic principles for validation was stated as follows

Quality, safety and effectiveness must be designed and built into the product.

Establish that the process equipment has the capability of operating within required parameters.

Demonstrate that controlling, monitoring and/or measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment.

Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been opted within the prescribed parameters for the process and that the output or product consistently meets the predetermined specifications for quality

Monitor the validated process during routine operation. As needed, re-qualify and rectify the equipment.

Once the process has been completely defined, equipment usually will be required to perform the actual processing of the product. It is collectively called “the system”. The system and its operations can then be identified and defined.[8]

BENEFITS:

- Reduces the risk of regulatory non- compliance.
- Reduction in rejections & reworks.
- Reduces the chances of product recall from the market

- Reduction of quality costs namely
    - ✓ Preventive costs
    - ✓ Appraisal costs
    - ✓ Internal failure costs
    - ✓ External failure costs
- May require less in-process control and end product testing; parametric release of batch can be done.
- More rapid & accurate investigations into process deviations.
- Assures smooth running of process.

REGULATORY BASIS OF VALIDATION:

The pre-requisites of validation are embodied with in the scope of existing cGMP regulations. According to USFDA current good manufacturing practices (cGMP)

- 21 CFR 211.110: control procedures shall be validate performance of the manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.
- 211.68- validation of computerized or automated processes
- 211.84(d)(2)- validation of supplier's test results for components when these test results are accepted inlieu of in-house testing after receipt.
- 211084(d)(3)- validation of supplier's test results containers and closures when these test results are accepted inlieu of in-house testing after receipt.
- 211.110(a)- validation of manufacturing processes to ensure batch uniformity and integrity of drug products.
- 211.113(b)- validation of sterilization processes.
- 211.165(e)- validation of analytical methodologies (explicity defines validation)

The principles and guidelines of GMP for EU were published in directive 2003/94/EC for human drugs. [6]

PROCESS VALIDATION:

It has been said that there is no specific basis for requiring a separate set of process validation guidelines, since the essentials of process validation are embodied with in the purpose and scope of the present cGMP regulations. The specific term process validation should be reserved for the final stages of the product/ process development sequence. [7] The schematic picture of process validation for a new/existing process/ product is shown in figure 3.

Validation master plan:

Validation master plan may be defined as internally approved document that describes in clear, unambiguous and concise wording, the general expectations, inventions, methods and approaches to be used during the entire validation effort.[3,11]

The ECE guide recommends the following contents in VMP

- ✓ Validation policy
- ✓ Organizational structure of validation activities
- ✓ Summary of facilities, systems, equipment and processes to be validated
- ✓ Documentation format (format to be used for protocols & reports)
- ✓ Planning & scheduling
- ✓ Change control
- ✓ Reference to existing documents. [4]

Validation protocol:

After preparing VMP, the next step is to prepare validation protocol. There are atleast the following contents in a validation protocol.

- ✓ Purpose and scope of validation
- ✓ Responsibilities & functioning of persons/organizational units involved in validation
- ✓ Type of validation to be conducted
- ✓ Number of process validation runs
- ✓ Quality of materials used in the process
- ✓ Description of process
- ✓ All major equipments to be used, their type/design and their installation & operational qualification
- ✓ Critical process parameters & operating ranges
- ✓ Sampling plans
- ✓ Specifications & test data to be collected
- ✓ Acceptance criteria to include that validation has been successful
- ✓ Measures to be taken in the event of process validation failure.[4]

Validation protocols define the extent of verification, testing & challenging activities along with their appropriate acceptance criteria, testing methods & data recording methods. The validation program and its protocols are generally divided into the following 4 phases.

- ❖ Design qualification (DQ) protocol:
  This document generally provide the means to verify that the proper process functional requirements have been incorporated into the basis for design for all engineered systems and are included as part of performance criteria for system hardware and software.
- ❖ Installation qualification (IQ) protocol:
  This document provides basis for verifying the proper installation of the designed system, in accordance with the design & engineering specifications.
- ❖ Operational qualification (OQ) protocol:
  This document provides basis for testing the components of a installed system to demonstrate conformance with the approved operational criteria.
- ❖ Performance qualification (PQ) protocol:

This document provides basis for challenging the proper performance of the whole-total system while operating as an integral part of the process.

Validation report:

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized. The report should include the following

- Title and objective of the study
- References to protocols
- Details of materials
- Equipment
- Programme and cycles used
- Details of procedures and tested methods
- Results (compared with acceptance criteria), and
- Recommendation on the limit and criteria to be applied on future basis.

RESPONSIBILITIES OF EACH ORGANIZATIONAL STRUCTURE:

Department	Responsibility
Engineering	Installation qualification & certification of plant, facilities, equipment & support system.
Development	Design, optimization & qualification of manufacturing process with in design limits, specifications and/or requirement
Manufacturing	Operation & maintenance of plant, facilities,

	equipment, support system & specific manufacturing process with in design limits, specifications and/or requirements.
Quality Assurance	Establishment of approvable validation protocols & conducting process validation by monitoring, sampling, testing, challenging and/or auditing specific manufacturing process for compliance with design limits, specifications and/or requirements. [6]

VALIDATION LIFE CYCLE:

process validation life cycle starts at the process design phase (process/product development) and continues through process verification (monitoring & assessment of process effectiveness) as stated by FDA's new guideline on process validation activities are carried out. Validation life cycle is shown in figure 2. [6,9]

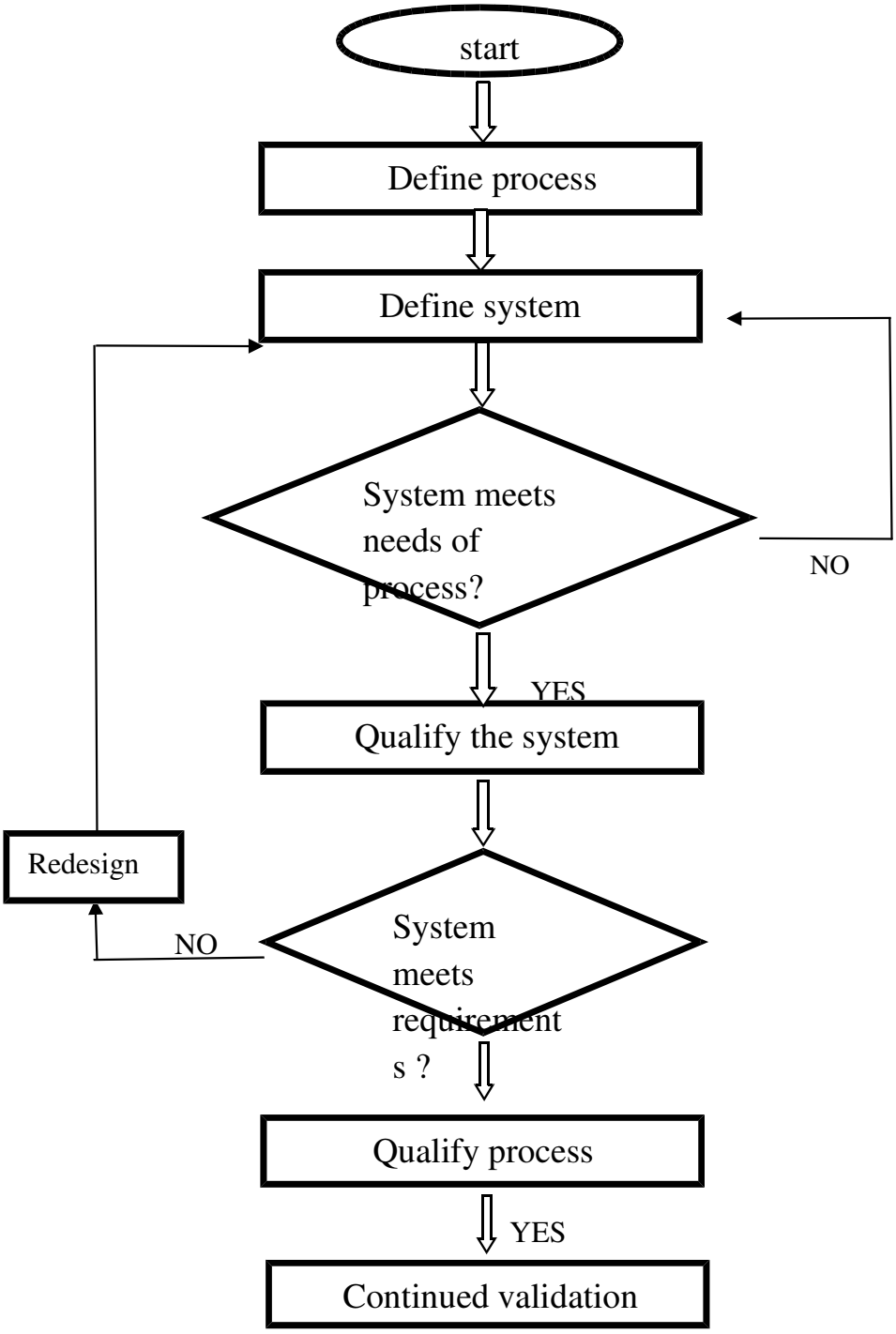
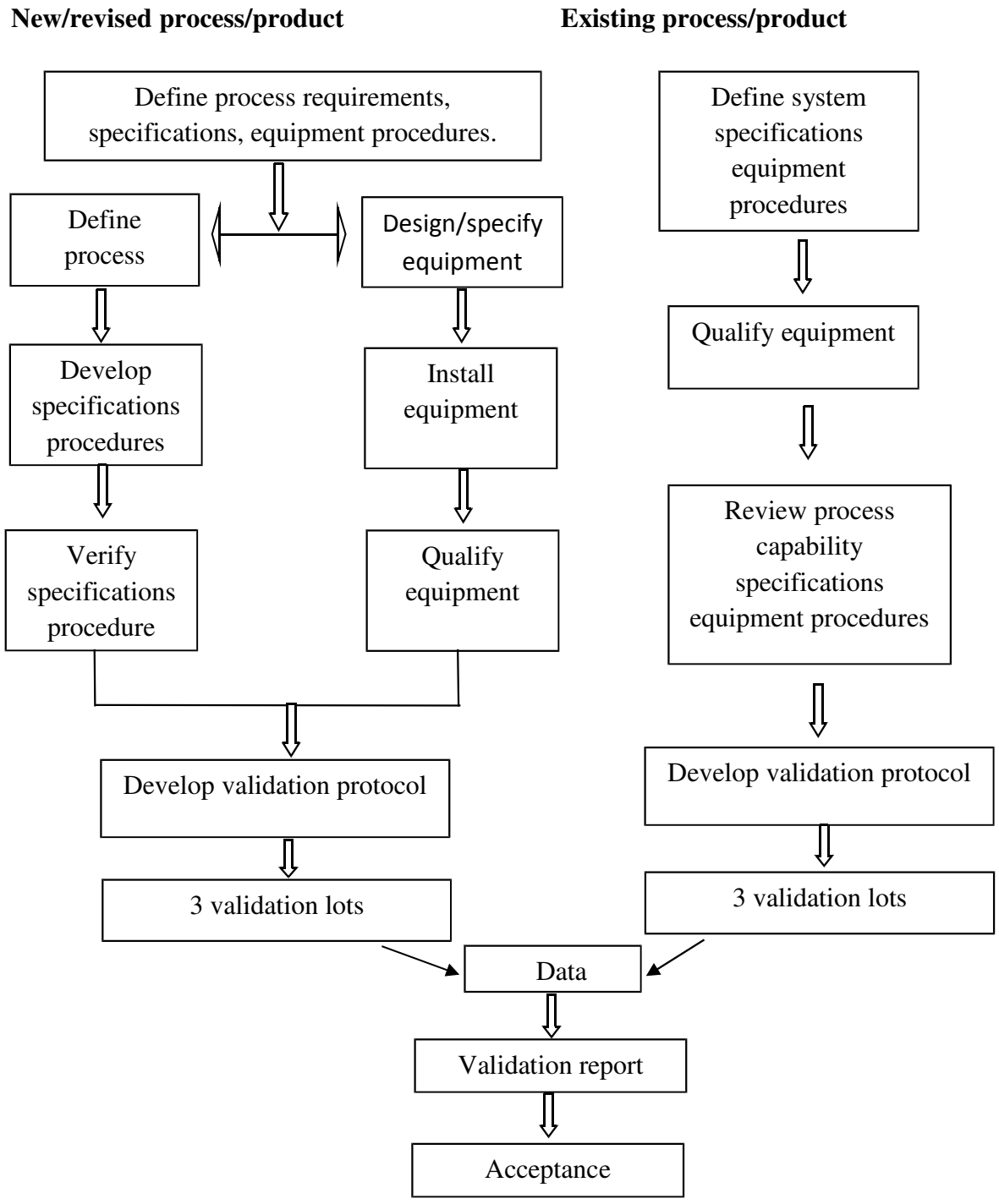

start
Define process
Define system
System meets needs of process?
NO
YES
Qualify the system
Redesign
NO
System meets requirements ?
Qualify process
YES
Continued validation

Fig:2 validation life cycle

Validation process schematic:



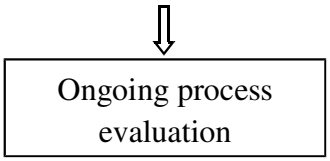


Fig:3 validation process of new and existing product/process[10]

WHAT SHOULD BE VALIDATED?

Any aspect of operation, including significant changes to premises. Facilities, equipment or processes, which may affect the quality of the product directly or indirectly should be qualified and validated.

Laboratory scale batches:

These are produced at the research & early development laboratory stage; they may be of very small size. These batches may find many uses, for example to support formulation & packaging development, clinical and/or pre-clinical studies.

Data derived from these batches assist in the evaluation & definition of critical product performance characteristics and there by enables the choice of appropriate manufacturing process.

Pilot batches:

These may be used in the process development or optimization stage, may be used to support formal stability studies and also to support pre-clinical & clinical evaluation. Pilot batch size should correspond to atleast 10% of the production scale batch i.e such that the multiplication factor for scale-up does not exceed 10.

For oral solid dosage forms this size should generally be 10% of the production scale or 1,00,000 units which ever is greater. The role of pilot scale batches is to provide data predictive of the production scale product. It may be necessary to further develop & optimize the manufacturing process using pilot scale batches. The pilot batch therefore provides the link between process development and industrial production of product. The purpose of the pilot batch is to challenge the method proposed for routine production i.e to analyze and evaluate the difficulties and critical points of manufacturing process, the apparatus and method most appropriate to large scale production.

Production scale batches:

These batches are of the size which will be produced during the routine marketing of the product. Data on production scale batches may not always be available prior to granting marketing authorization. Where production scale data are not available or presented at the time of submission, the two stage approach outlined below should be followed.

First a thorough evaluation & characterization of the critical process parameters at laboratory or pilot scale, followed by a formal validation programme on production scale batches for which the scheme has been described to the regulatory authorities in the dossier and for which the results can be subsequently verified by supervising authority according to national procedure.

PROCESS VALIDATION PHASES:

Phase 1 (process capability design):

FDA in its process validation guidelines states that a manufacturer should evaluate all factors that affect product quality when designing and undertaking a process validation study.

Process capability is the carrying out of studies to determine [6]

- The number & relative importance of critical process parameters that influence process output
- The numerical values or ranges for each of the critical process parameters that result in acceptable process output.

If the process capability is properly defined, the process should result into output of consistent attributes when operated with in the defined limits of critical process parameters.

Phase 2 (process validation phase or process qualification phase):

It is designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under worst case conditions. It represents the actual studies or trials conducted to show

- That all systems, sub-systems or unit operations of a manufacturing process perform as intended
- That all critical parameters operate with in their assigned control limits
- That such studies & trials which form the basis of process capability design & testing, are verifiable and certifiable through proper documentation.

Phase 3 (validation maintenance phase):

It requires frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process and that all SOPs have been followed including change control procedures. At this stage the validation team also assures that there have been no changes/deviations that should have resulted in re-qualification & re-validation.

TYPES OF PROCESS VALIDATION:

Depending on when it is performed in relation to production, validation can be prospective, con-current, retrospective and revalidation. [6]

- **Prospective validation:**
  Prospective validation is usually undertaken whenever a new formula, process and/or facility need to be validated before routine pharmaceutical production starts. It is also usually employed when sufficient historical data is either unavailable or insufficient and in-process and final product testing is inadequate to ensure high degree of confidence for quality characteristics and reproducibility. Regulatory authorities favours prospective validation for obvious reason of higher degree of confidence and minimal risk, as it ensures process to be under control and effective prior to manufacture or release of product. Nevertheless, higher degree of confidence is also associated with higher cost of operation. Therefore, a due consideration must be given to regulatory authority's preference and cost to benefit analysis (when alternate type of validation is possible).
- **Concurrent validation:**
  Concurrent validation is appropriate when

- ✓ It is not possible to complete a validation programme before routine manufacturing starts and it is known in advance that finished products will be for sale.
- ✓ It is more appropriate to validate process during routine production due to well understanding of process.
- ✓ Extensive testing and monitoring ensures the desired quality characteristics of product with high degree of confidence.

Extensive testing and monitoring during concurrent validation may verify quality attributes of the product of particular batch, but does not provide high degree of assurance that subsequent batches processes under some condition and parameter will attain same quality attributes.

❖ Retrospective validation:

There are many processes in use in many companies that have not undergone a formally documented validation process. Validation of these processes is possible provided sufficient historical data is available to provide documentary evidence that various processes are considerably stable and are doing what they are believed to do.

A large historical data set available may provide higher confidence and better picture than data generated from few trail runs in prospective validation. This type of validation is acceptable only for well established processes and where quality attributes and critical process parameters have been identified and documented. Appropriate in-process specifications and controls have been established and documented. And there have not been excessive process / product failures attributable to causes other than operator error or equipment failure unrelated to equipment suitability.

The number of batches to review will depend on the process but in general data from 5 to 10 consecutive batches should be examined to assess process consistency. The review should include any batches that failed to meet specifications. However any discrepancies or failure in the historical data may be excluded provided there is sufficient evidence that the failure was caused by isolated occurrences.

The source of this validation may include batch documents, control charts, maintenance log books, records of personnel changes, process capability studies, finished product data including trend cards and storage stability studies.

❖ Revalidation:

Re-validation is needed to ensure that the changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality.

Re-validation may be divided in to two broad categories:

- Re-validation after any change having a bearing on product quality.
- Periodic re-validation carried out at scheduled intervals.

Revalidation after changes:

Revalidation must be performed on introduction of any changes affecting a manufacturing and/or standard procedure having a bearing on the established product performance characteristics. Such changes may include those in starting materials, packaging materials, manufacturing process, equipment, in-process controls, manufacturing area or support systems (water, steam etc). Every such change requested should be reviewed by a qualified validation group which will decide whether it is significant enough to justify revalidation and if so, its extent.

Re-validation after changes may be based on the performance of the same tests and activities as those used during the original validation including tests on sub

processes and on the equipment concerned. Some typical changes which require revalidation include the following

* **Changes in the starting materials:**
  Changes in the physical properties such as density, viscosity, particle size distribution, crystal type and modification of the active ingredients or excipients may effect the mechanical properties of the material, as a concequence they may adversely affect the process or the product.
* **Changes in the packaging material:**
  Example replacing plastics by glass may require changes in the packaging procedure and therefore effect the product stability.
* **Changes in the process:**
  Changes in the mixing time, drying temperature and cooling regime may effect subsequent process steps and product quality.
* **Changes in equipment:**
  Measuring instrument may effect both the process and the product. Repair and maintenance work such as replacement of major equipment components may effect the process.
* **Changes in the production area and support system:**
  The rearrangement of manufacturing area and/or support systems may result in changes in the process. The repair and maintenance of support systems such as ventilation may change the environmental conditions and as a consequence revalidation/requalification may be necessary mainly in the manufacture of sterile products.

- **Periodic revalidation:**

It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly equipment wear may also cause gradual changes. Consequently revalidation at scheduled times is advisable even if no changes have been deliberately made.

The decision to introduce periodic revalidation should be based on a review of historical data i.e data generated during in-process and finished product testing after the latest validation, aimed at verifying that the process is under control.

2. LITERATURE REVIEW

- **Chawla Nirmaljot singh et-al [13] ;** has overviewed role of process validation of tablet manufacturing process. It often includes qualification of systems & equipment. For each type of pharmaceutical dosage form there are various stages in manufacturing process that need to be qualified inoder to validate the complete process.
- **Rajkumar P.Patil [14];** has explored the understanding of blend uniformity in the manufacture of solid oral dosage forms under c GMP. He concluded that testing final blend uniformity as a suitable in-process control may evaluate and highlight

the incoming ingredient batch to batch differences as well as the physical variations in different lots of active materials.

- **Wayne A.Taylor [15] ;** described the application of many statistical tools like control charts, capability studies, designed experiments, tolerance analysis, robust design methods, failure mode and effect analysis, sampling plans, mistake proofing in validation.
- **Satyabrata Jena et-al [16];** have done overview on the process validation of solid dosage forms, protocol preparation and regulatory basis for process validation with special emphasis on tablets in industry. It gives in detail the validation of each step of the manufacturing process through wet granulation. They concluded that Solid dosage form validation should be part of a comprehensive validation program within an industry. The total program should begin with validation of the active pharmaceutical ingredient (API) characteristics so that this material will be uniform batch after batch, providing a solid footing upon which the dosage form will be built. Continued awareness of validation requirements and a diligent application of validation principles will thus help to ensure that pharmaceutical products will be able to be developed and produced with the quality and reproducibility required from regulatory agencies across the world.
- **Garg R et-al [17];** has described guidance for validation of solid dosage forms, sterile products, oral solutions and suspensions. They gave an overview on aspects of validation in terms of pharmaceutical unit operations, i.e that individual technical operation that comprises various steps involved in product design and evaluation.
- **Beer TR et-al [18];** studied a strategy to implement a Process Analytical Technology (PAT) system in the blending step of tablet production system.

Raman spectroscopy was used as a PAT tool for end point control of powder blending process. It was observed that the ratio between the blending times and the measurement intervals should be sufficiently high to be able to study the critical effects properly.

- **Chitlange S et-al [19];** provided information on validation of granulation process which involved validation of equipments utilized in manufacturing of granulation and validation of operation carried out for granulation. It also validate final product for bulk density, moisture content, particle size distribution etc. successfully validating a process may reduce the dependence upon intensive inprocess and finished product testing.
- **Elsie Jatto et.al [20];** have done overview of pharmaceutical validation and process controls in drug development. It has been known that facilities and processes involved in pharmaceutical production impact significantly on the quality of the products. The processes include raw material and equipment inspections as well as in-process controls. Process controls are mandatory in GMP. The purpose is to monitor the on-line and off-line performance of the manufacturing process and hence, validate it. Thus validation is an integral part of quality assurance. This overview examines the need for pharmaceutical validation, the various approaches and steps involved and other pertinent considerations.
- ***Andrew W. Jones*** [21] discussed how to validate a process by introducing some basic statistical concepts to use when analyzing historical data from Batch Records and Quality Control Release documents to establish specifications and quality attributes for an existing process.
- **Dusel-RG et-al [22];** performed food and drug administration requirements regarding manufacturing process validation were discussed including examples of

different types of documentation to fulfill the requirements of minimal or extensive records.

- **O'-shea-et-al [23];** have done an overview of validation in the pharmaceutical industry including legal, ethical, developmental & economic considerations and also included validation process for granulating, blending and tableting a product.
- **Edwards-CM et al [24];** have done process validation of the manufacturing of solid dosage forms was discussed including protocols, records to be maintained, suitability of raw materials, equipment performance qualification, the number of validation runs required and acceptance criteria.

3. AIM & OBJECTIVE OF STUDY

- The present study is carried out at Orchid Healthcare, Irrungattukottai. The company is involved in the manufacturing and distribution of wide range of pharmaceutical products.
- The aim of the present work is to define the validation process for an Anti convulsant tablet 750mg and to manufacture 3 validation batches of 3,00,000 tablets as per the approved batch manufacturing record.
- To evaluate and qualify the consistency of Anti convulsant tablet 750mg
- The objective in process validation was to validate critical processes like granulation, drying, blending, compression & coating and to establish documented evidence that product when manufactured at production scale operation meets all the quality and design specifications.

4. PLAN OF WORK

Process validation is carried for the following product.

Anti convulsant tablet 750mg

Three consecutive batches should be manufactured for the validation of anti convulsant tablet 750mg.

The following plan of work is designed based on Master Manufacturing formula

1. Literature review
2. Preparing process flow chart
3. Preparing the validation protocol which include
    - Review of qualification status of equipment & facility
    - Identification of CCPs & CQAs
    - Preparation of sampling plan
    - Acceptance criteria
4. Execution of validation
5. Compilation & evaluation of the results.

5. DRUG PROFILE

The present drug of study is an anti convulsant tablet

Description:

This anti convulsant drug is a white to off-white crystalline powder with a faint odor and a bitter taste.

Solubility:

- It is very soluble in water (104.0 g/100 mL).
- It is freely soluble in chloroform (65.3 g/100 mL) & in methanol (53.6 g/100 mL)
- soluble in ethanol (16.5 g/100 mL)
- sparingly soluble in acetonitrile (5.7 g/100 mL).
- practically insoluble in n-hexane.

(Solubility limits are expressed as g/100 mL solvent.)

Indications and usage:

- indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy.
- indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy.
- indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.

Available strengths:

The present drug of study is available in 250mg, 500mg, 750mg & 1000mg strengths.

Mechanism of action:

Mechanism unknown; may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity ; thought to stimulate synaptic vesicle protein 2A (SV2A), inhibiting neurotransmitter release.

Pharmacokinetics

Absorption

T_{max} is 1 h. Oral bioavailability is 100%. Food does not affect the extent of absorption, but it can decrease C_{max} 20% and delay T_{max} 1.5 h. Steady state is achieved after 2 days of multiple, twice-daily dosing.

Distribution

Less than 10% is protein bound. Vd is close to the volume of intracellular and extracellular water.

Metabolism

Not extensively metabolized. Major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite ucb L057.

Elimination

Plasma half-life is approximately 7 h. It is eliminated from the systemic circulation by renal excretion as unchanged drug, which represents 66% of dose.

Drug interactions:

Carbamazepine

Increased risk of carbamazepine toxicity, unrelated to elevated plasma concentrations, has been reported.

Probenecid

The C_{max} of the inactive metabolite of this anti convulsant drug is approximately doubled.

Adverse reactions:

The most common adverse effects occurring with this drug were CNS related and included somnolence, asthenia, and dizziness.The frequency of these symptoms was higher in patients started on higher dosages (> 1000 mg/day)

Process stage	**Process variable**	**samples**				**Testing needed**
		No. of samples to be taken	**Type of containers**	**Sample size**	**No. of samples to be tested**	
Drying	Dried granules of batch at an inlet temperature of 60 ±5 ℃ for 10 min in FBD till the	1 pooled sample If LOD is 1.5 – 3.0%	Glass vial	1 gm at each location	1 pooled sample for every 10 min till LOD shall be 1.5-3% w/w	LOD

	LOD shall be 1.5 – 3%	5 samples If LOD is 1.5 – 3.0%		1 gm at each location	5 samples after attaining LOD shall be 1.5-3% w/w	
Blending	blend	10 samples in duplicate	Glass vial	1050 mg to 3150mg Die size:5ml	10	Content uniformity
	Blending time Pre lubrication:10 min Post lubrication:5 min Blend rpm:15 rpm	3 samples	Poly bag	Each 100 gm	03	Bulk density, Particle size distribution
	After unloading the blend from blender in to SS bin	10 samples in duplicate from SS bins	Glass vial	1050 mg to 3150mg Die size:5ml	10	Content uniformity
		1 pooled sample from all SS bins	Poly bag	25 gm	01	Description, assay, water content

Table: 4 sampling plan

Process stage	**Process variable**	**samples**		**Testing needed**
		No. of samples to be taken	**Type of containers**	
	Compression speed *min. set speed:10rpm	50 tablets	Poly bags	Weight of 10 tablets Disintegration Thickness Weight variation hardness Friability Physical inspection

Compression	Compress about 30,000 tablets	Pooled sample of 50 tablets from the containers	Poly bags	Dissolution UOD
	*Max. set speed:18rpm Compress about 30,000 tablets	50 tablets	Poly bags	Weight of 10 tablets Disintegration Thickness Weight variation hardness Friability Physical inspection
		Pooled sample of 50 tablets from the containers	Poly bags	Dissolution UOD
	*Optimum speed:15rpm	Pooled sample of 50 tablets shall be collected from corresponding IPC during 1/3rd to 2/3rd level of hopper	Poly bags	Weight of 10 tablets Disintegration Thickness Weight variation hardness Friability Physical inspection
		Pooled sample of 50 tablets from the containers	Poly bags	Dissolution UOD

Table: 4 sampling plan (contd…)

Process stage	Process variable	samples		Testing needed
		No. of samples to be taken	**Type of containers**	
compression	*Optimum speed:15rpm	Pooled sample of 50 tablets shall be collected from corresponding IPC during 2/3rd to end level of hopper	Poly bags	Weight of 10 tablets Disintegration Thickness Weight variation hardness Friability Physical inspection
		Pooled sample of 50 tablets from the containers	Poly bags	Dissolution UOD
coating	Description	Pooled sample	Poly bags	Physical appearance
	Weight build up	50 tablets	Poly bags	Weight build up
	Spary gun angle	NA	NA	NA
		Pooled sample of 50 tablets from all the containers	Poly bags	Dissolution profile on 12 tablets
		Pooled sample of 250 tablets from all the containers	Poly bags	Description Identification by HPLC, IR, chiral HPLC Water content Avg weight Uniformity of dosage units by wt. variation Dissolution Assay Related substances

*samples shall be taken from both the sides & tested atleast for two time intervals

Process stage	Process variable	samples		Testing needed
		No. of samples to be taken	**Type of containers**	
Tablet counting/filling	Minimum speed Maximum speed Target set speed	10	HDPE containers 120s count	Verification of fill bottle count

Induction sealing	Induction power supply set	05	HDPE container 150cc and Child Resistant Closure	Visual inspection for seal integrity
Labeling	Minimum speed Maximum speed Target set speed	10	HDPE container 150cc Self adhesive printed container label 120s count	Visual inspection

Table: 4 sampling plan (contd…)

6.2.5 SAMPLING PROCEDURE AT DIFFERENT STAGES:

- **Drying:**

  Moisture content of the dried granules has to be established during the validation of drying process. One pooled sample was taken for every 10min till the LOD shall be 1.5% -3.0%. 5 samples were taken from 5 different locations in FBD after attaining the desired LOD to determine the moisture content.

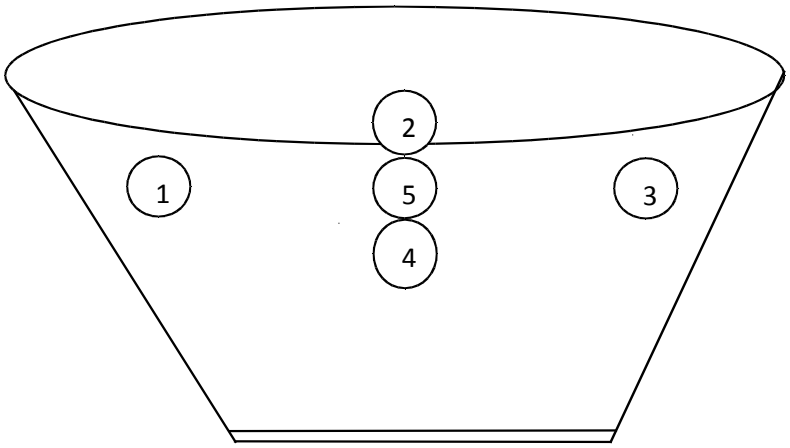


Fig: 6 Side View of Fluid Bed Dryer (FBD)

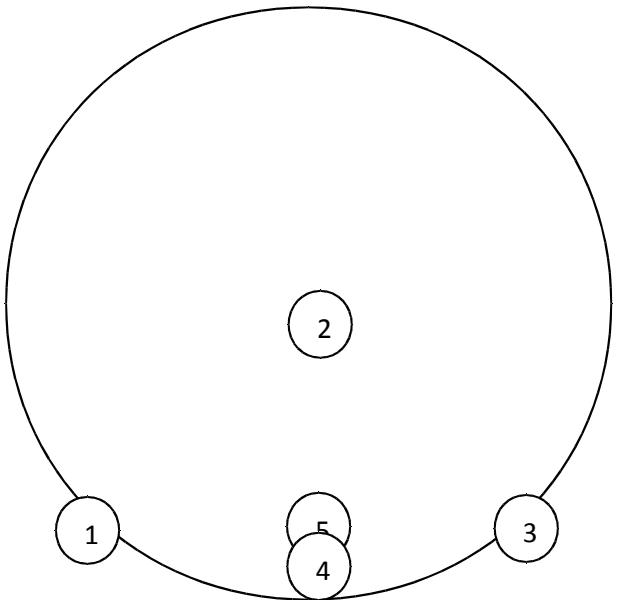


Fig: 7 Top View of Fluid Bed Dryer (FBD)

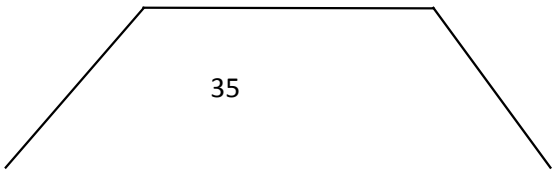
Location 1 : Left side of the FBD
Location 2 : Rear side of the FBD
Location 3 : Right side of the FBD
Location 4 : Front side of the FBD
Location 5 : Center of the FBD

- **Blending:**

  Content uniformity of the blend has to be established during the validation of blending process. 10 samples in duplicate were taken from different locations in the octagonal blender and tested for the content uniformity. Sample size (1050mg-3150mg) is average weight of each tablet to thrice of the average tablet weight. 3 samples were collected from right, middle & left sides of the octagonal blender for determination of bulk density and particle size distribution.

Sampling in SS bins: After loading the blend in to SS bins from the blender 10 samples in duplicate were taken to determine the content uniformity and 1 pooled sample from all the bins was taken for description, assay and water content.

10 samples in duplicate (20 samples) for Content uniformity



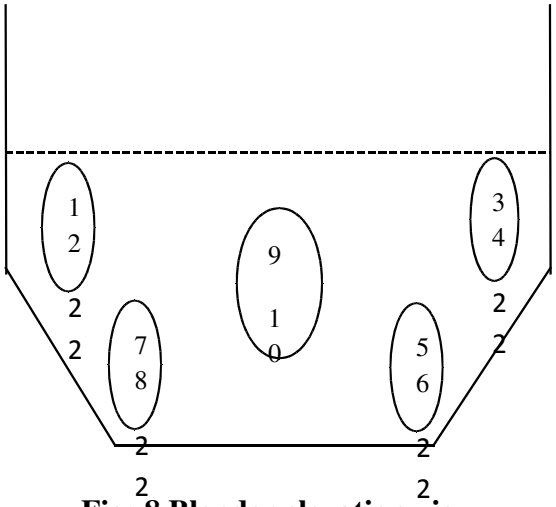
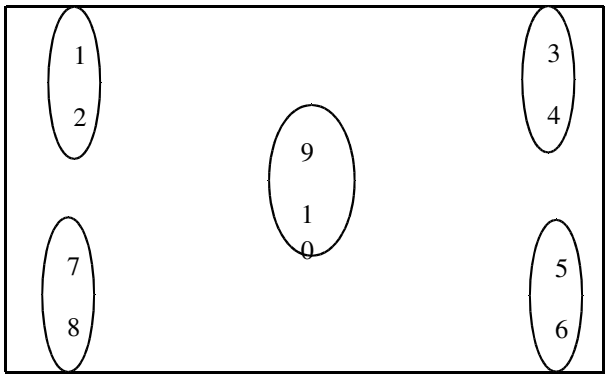
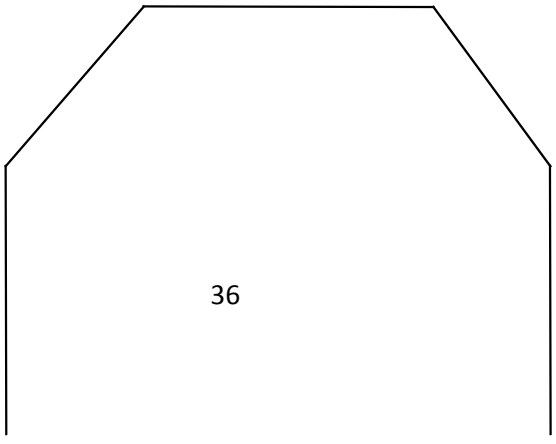


Fig: 8 Blender elevation view

Fig: 9 Blender top view



Three samples from different locations for Bulk density & Particle size distribution



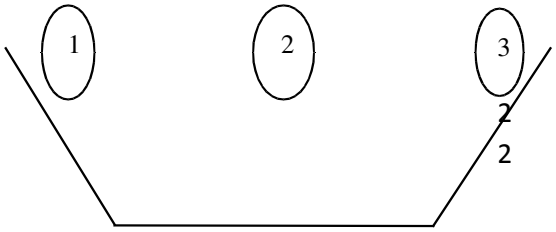


Fig: 10 Blender elevation view

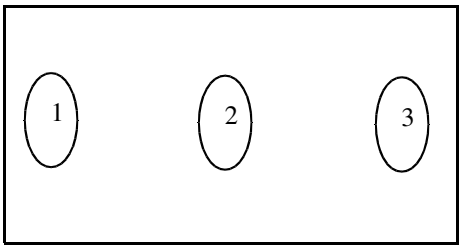


Fig: 11Blender top view

Location 1 : Left side of the Octagonal blender
Location 2 : Middle of the Octagonal blender
Location 3 : Right side of the Octagonal blender

Sampling plan - SS Bin

10 samples in duplicate (20 samples) for Content uniformity

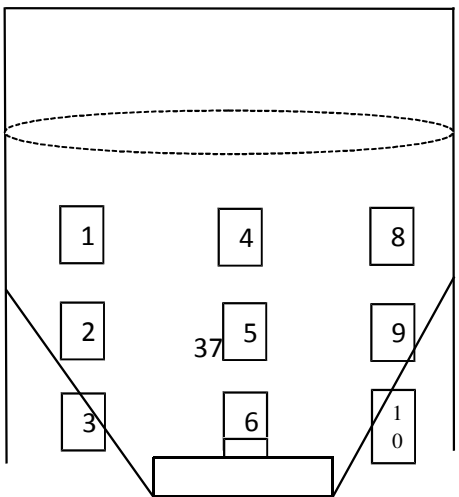


Fig: 12 Bin elevation view

One pooled sample for Description, Assay & Water content

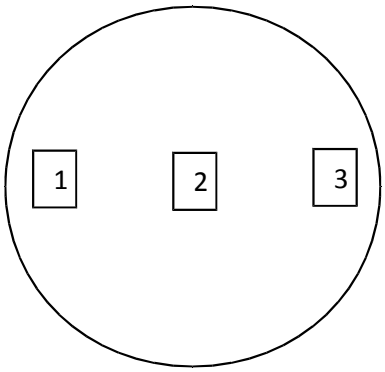


Fig: 13 Bin plain view

Compression:

Compression of 30,000 tablets each were carried out at minimum (10 rpm) and maximum (18 rpm) speeds.50 tablets at each speed were sampled from both the sides and tested for physical inspection, weight of 10 tablets, weight variation, thickness, hardness, friability & disintegration. Dissolution & UOD was carried out for pooled sample of 50 tablets from different containers. Machine speed was optimized at 15 rpm and pooled sample of each 50 tablets were collected from the

corresponding in-process container during 1/3rd to 2/3rd level of hopper & 2/3rd to end level of the hopper; tested for physical inspection, weight of 10 tablets, weight variation, thickness, hardness, friability & disintegration. Dissolution & UOD was also carried out for pooled sample of 50 tablets from the containers.

Coating:

Coating was carried out for three lots of compressed tablets to achieve the weight build up of 2.0%–3.0%. 50 coated tablets were sampled and tested for physical description, weight build up. Pooled sample of 50 coated tablets were collected from different containers and dissolution profile on 12 tablets was carried out. Similarly pooled sample of 250 tablets were collected and finished product analysis (description, identification, water%, average weight, uniformity of dosage units by weight variation, dissolution, assay, related substances) was carried out.

Packing:

Tablet counting & filling:

120 tablets were counted and filled in HDPE containers 150 cc at three different speeds; minimum (20 containers/min), maximum (40 containers/min), optimum (30 containers/min) speed. 10 containers were collected at each speed for verification of fill bottle count.

Induction sealing:

Induction sealing of HDPE 150 cc containers with CR closures were carried out with induction power supply was set at 70%. 5 bottles were sampled and checked for seal integrity

- **Labeling:**

Labeling of HDPE containers 150cc containing 120 tablets were carried out at minimum (20 containers/min), maximum (40 containers/min), optimum (30 containers/min) speeds. 10 bottles were collected at each speed for physical inspection.

6.2.6 JUSTIFICATION FOR SAMPLING POINTS:

Fluid bed dryer:

During the drying process hot air will be blown from the bottom and there may not be uniform flow of air due to which improper drying may occur. Hence samples will be taken at 5 different locations to check the moisture content

Octagonal blender:

Sampling points 1,2,3,4,5,6,7,8 are considered as dead spots in the octagonal blender as the baffle will not be in the contact with the blend at those points hence samples were taken to check the content uniformity. Sampling points 9, 10 are in direct contact with the baffle hence samples were taken to check the content uniformity as over mixing may lead to segregation of the particles.

Three samples were taken at middle, right and left sides of the blender to check the bulk density & particle size distribution as there may be segregation of particles during mixing.

SS BIN:

After blending, blend was transferred from octagonal blender in to SS bins. During the transfer more denser particles may settle at the bottom of the bin and also particles may segregate. Hence samples were taken at various locations from the SS bins to check the content uniformity

Pooled samples were taken to represent all the layers of the blend and tested for description, assay and water content.

- Duplicate samples were taken to rule out the analytical variations.

- Sample size is twice the quantity required for testing.

7. RESULTS

7.1 Stage: sifting

Visual inspection after sifting of raw materials were carried out and the results are shown in the table 5

Table: 5 sifting of raw materials

Test	Process control	Acceptance criteria	Batch No.		
			719B001	**719B002**	**719B003**
Visual inspection	Sifting of raw material	Absence of any lumps or foreign matter after sifting of raw material	complies	complies	complies

7.2 Stage: Granulation

CCPs monitored during granulation & results of granule formation for 3 batches are given in table 6

Table: 6 Results of granulation

Batch no.	Dry mixing time(minutes)	Main motor amperage at 75 rpm	Binder addition time at 100 rpm (minutes)	Main motor amperage	Granule formation
719B001	10	16.03	2	17.21	satisfactory
719B002	10	15.92	2	17.21	satisfactory
719B003	10	16.13	2	17.23	satisfactory

7.3 Stage: Drying

LOD at various locations are tabulated in table 7

Table: 7 % Loss on drying

	LOCATIONS				
Batch no.	**01**	**02**	**03**	**04**	**05**
719B001	2.2%	2.1%	2.15%	2.15%	2.15%
719B002	2.05%	2.2%	2.4%	2.3%	2.05%
719B003	1.9%	2.25%	2.25%	2.3%	2.05%
Acceptance criteria = 1.5 to 3%					

% LOD from 3 batches is shown graphically in fig 14

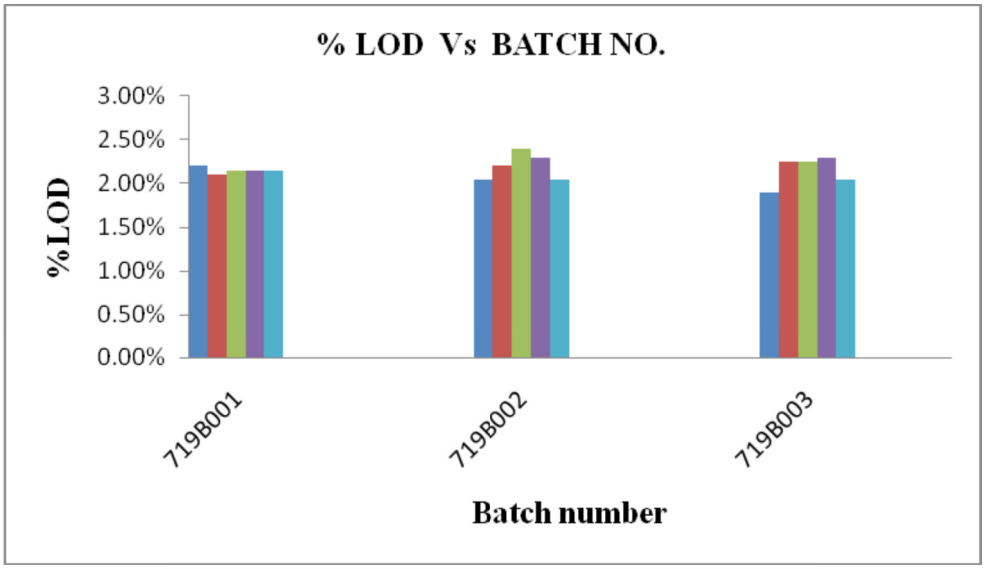


Figure: 14 % Loss on drying in different batches

7.4 Stage: BLENDING

7.4.1Sampling location: Octagonal blender

Results of content uniformity at various locations in the blender are given table 8 and it is represented graphically in fig 15

Table: 8 % Content uniformity from octagonal blender

Locations	Batch no.			Acceptance criteria
	719B001	719B002	719B003	
1.	100.2	99.2	100.6	
2.	101.5	99.2	101.7	
3.	100.0	98.7	101.9	
4.	100.6	99.2	100.9	
5.	99.9	99.2	102.2	
6.	100.6	99.2	100.5	

7.	100.2	99.2	101.5	**NLT 90.0 % to NMT 110.0 % of the labeled amount.**
8.	99.9	98.8	100.9	
9.	102.7	98.3	100.9	
10.	100.2	98.1	100.1	
	99.9	98.1	100.1	
Max.	102.7	99.2	102.2	
Average	100.58	98.91	101.12	
RSD	**0.9**	**0.3**	**0.6**	**RSD: NMT 5%**

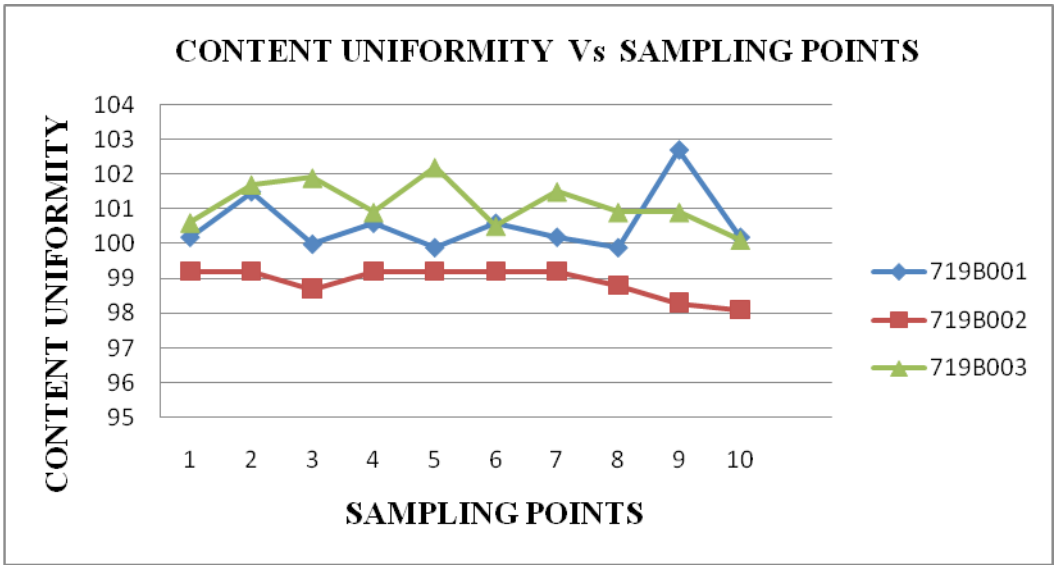


Figure: 15 CONTENT UNIFORMITY FROM OCTOGONAL BLENDER

Results of density (apparent & tapped) of blend at various locations in the blender are given

table 9

Table: 9 Density of blend

Test	Sampling location: Octagonal blender (left side)		
	Batch no 719B001	Batch no.719B002	Batch no. 719B003
Apparent density (g/ml)	0.59	0.57	0.59
Tapped density (g/ml)	0.71	0.61	0.61
Test	**Sampling location: Octagonal blender (middle)**		
	Batch no. 719B001	Batch no.719B002	Batch no. 719B003
Apparent density (g/ml)	0.59	0.57	0.59
Tapped density (g/ml)	0.71	0.69	0.69
Test	**Sampling location: Octagonal blender (right side)**		
	Batch no. 719B001	Batch no.719B002	Batch no. 719B003
Apparent density (g/ml)	0.59	0.57	0.59
Tapped density (g/ml)	0.71	0.69	0.69

Results of particle size distribution of blend at various locations in the blender are given table 10, 11, 12 and are represented graphically in fig 17, 18, 19 respectively.

Table: 10 particle size distribution of blend from left side of the blender

Sampling location: Octagonal blender (left side)

Sieve ID no.	% of material retained on ASTM sieve		
	Batch no. 719B001	**Batch no. 719B002**	**Batch no. 719B003**
#20	5.30	6.35	6.24
#30	11.59	13.44	13.79
#40	15.89	18.94	19.18
#60	22.94	26.44	26.57
#80	28.59	33.48	33.27
#100	36.38	39.49	39.46
#200	53.02	54.07	54.15
Cumulative material collected	99.50	99.90	99.70

Table: 11 particle size distribution of blend from middle of the blender

Sampling location: Octagonal blender (middle)

Sieve ID no.	% of material retained on ASTM sieve		
	Batch no. 719B001	**Batch no. 719B002**	**Batch no. 719B003**
#20	5.50	5.69	6.35
#30	12.39	13.04	13.59
#40	17.09	17.53	19.19
#60	23.79	25.02	26.54
#80	29.54	32.67	33.83
#100	36.03	38.51	40.18
#200	52.32	53.40	54.77
Cumulative material collected	99.55	99.50	99.65

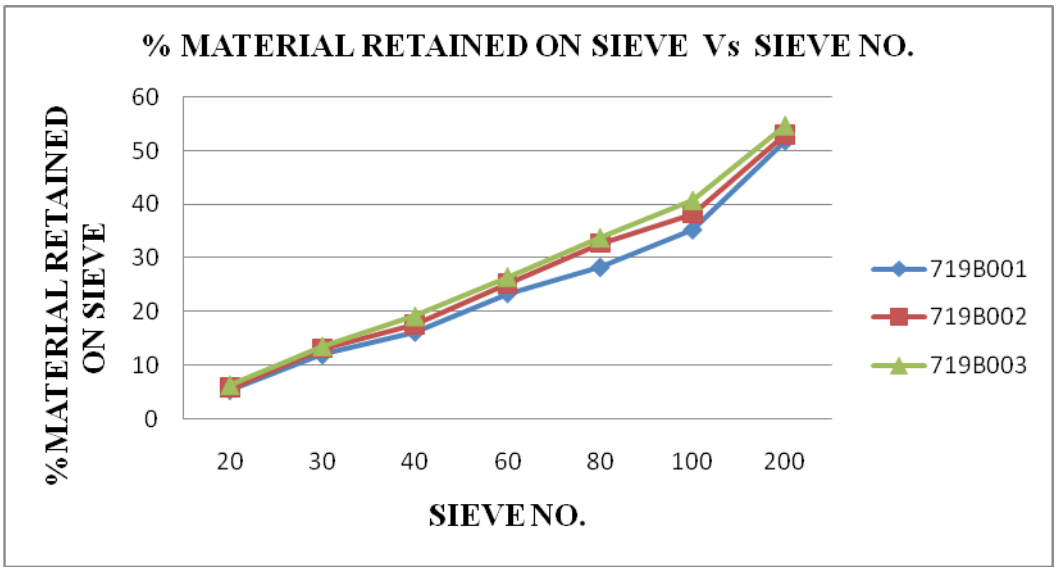

% MATERIAL RETAINED ON SIEVE Vs SIEVE NO.
%MATERIAL RETAINED ON SIEVE
60
50
40
30
20
10
0
20
30
40
60
80
100
200
SIEVE NO.
719B001
719B002
719B003

Fig: 17 PARTICLE SIZE DISTRIBUTION FROM LEFT SIDE OF BLENDER

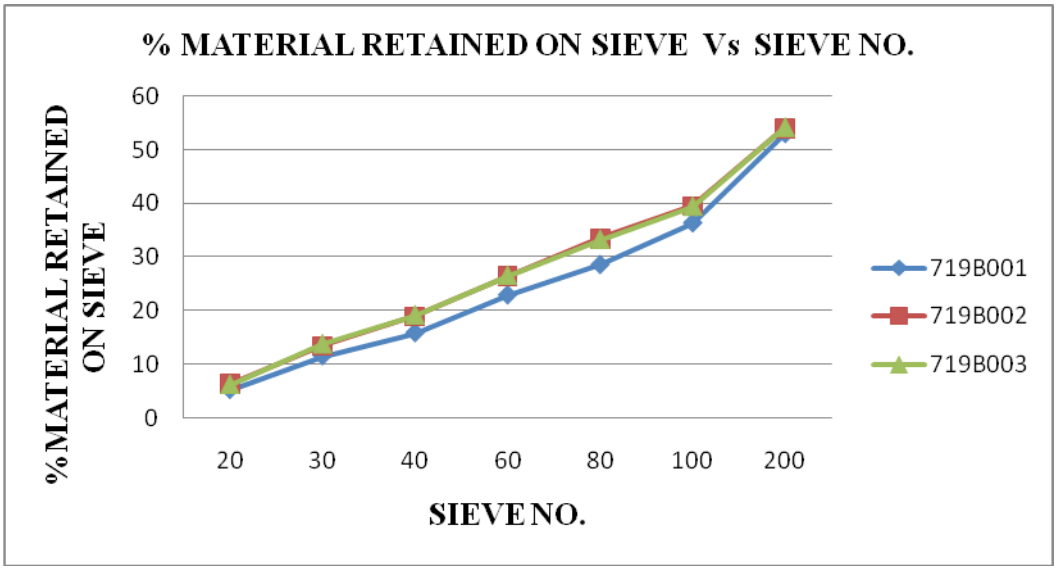


Fig: 18 PARTICLE SIZE DISTRIBUTION FROM MIDDLE OF BLENDER

Table: 12 particle size distribution of blend from right side of the blender

Sampling location: Octagonal blender (right side)

Sieve ID no.	% of material retained on ASTM sieve		
	Batch no. 719B001	**Batch no. 719B002**	**Batch no. 719B003**
#20	5.35	5.80	6.35
#30	11.95	13.14	13.59
#40	16.20	17.64	19.19
#60	23.40	25.29	26.54
#80	28.25	32.78	33.83
#100	35.25	38.28	40.8
#200	51.80	53.07	54.77
Cumulative material collected	99.75	99.70	99.65

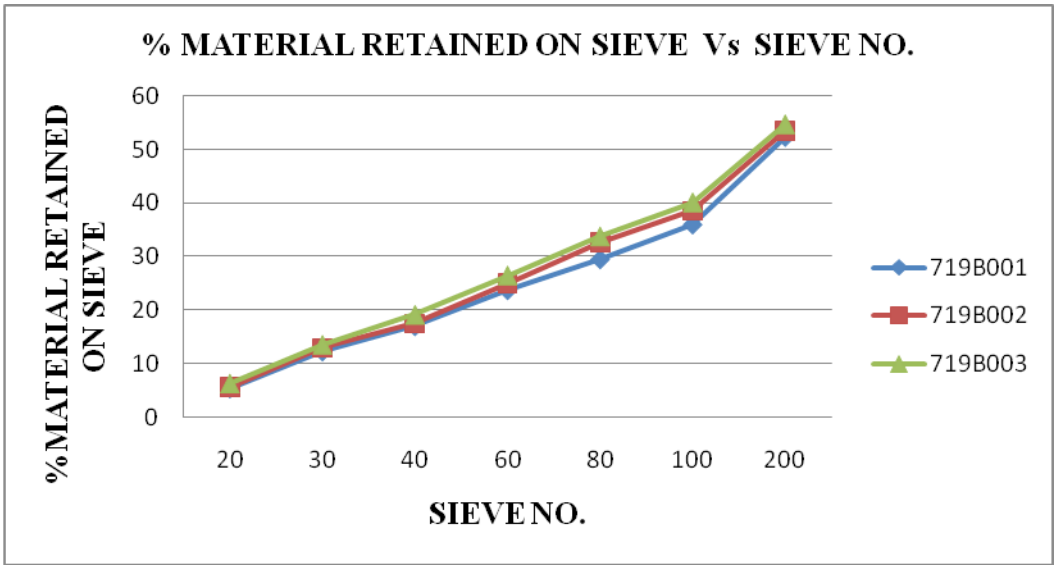


Fig: 19 PARTICLE SIZE DISTRIBUTION FROM RIGHT SIDE OF BLENDER

Stage: BLENDING

7.4.2 Sampling location: SS bin

Results of pooled sample of blend from SS bin are shown in table 13

Table: 13 Description, %water content & assay of pooled sample of blend from SS bin

Test	Acceptance criteria	Batch No.		
		719B001	**719B002**	**719B003**
Description	White to off white granular powder	White granular powder	White granular powder	White granular powder
Water content by KF (%w/w)	NMT 3%	2.0%	1.6%	2.0%
Assay	Tablet blend contains the equivalent of NLT 95% and NMT 105% of the labeled amount	98.9%	99.6%	99.3%

Stage: BLENDING

Sampling location: SS bin

Results of content uniformity of blend from SS bin are tabulated in table 14 & shown graphically in fig 16

Table: 14 % Content uniformity of blend from SS bin

Locations	**Batch no.**			**Acceptance criteria**
	719B001	**719B002**	**719B003**	
1.	100.2	99.4	100.6	

2.	99.9	99.3	100.9	**NLT 90.0 % to NMT 110.0 % of the labeled amount.**
3.	103.0	99.0	101.5	
4.	101.0	99.1	101.3	
5.	101.1	100.4	100.6	
6.	100.9	99.7	100.0	
7.	100.1	98.8	100.9	
8.	100.5	99.0	100.9	
9.	100.4	99.3	99.1	
10.	100.2	99.8	101.3	
	99.9	98.8	99.1	
Max.	103.0	100.4	101.5	
Average	100.73	99.38	100.71	
RSD	**0.9**	**0.5**	**0.7**	**RSD: NMT 5%**

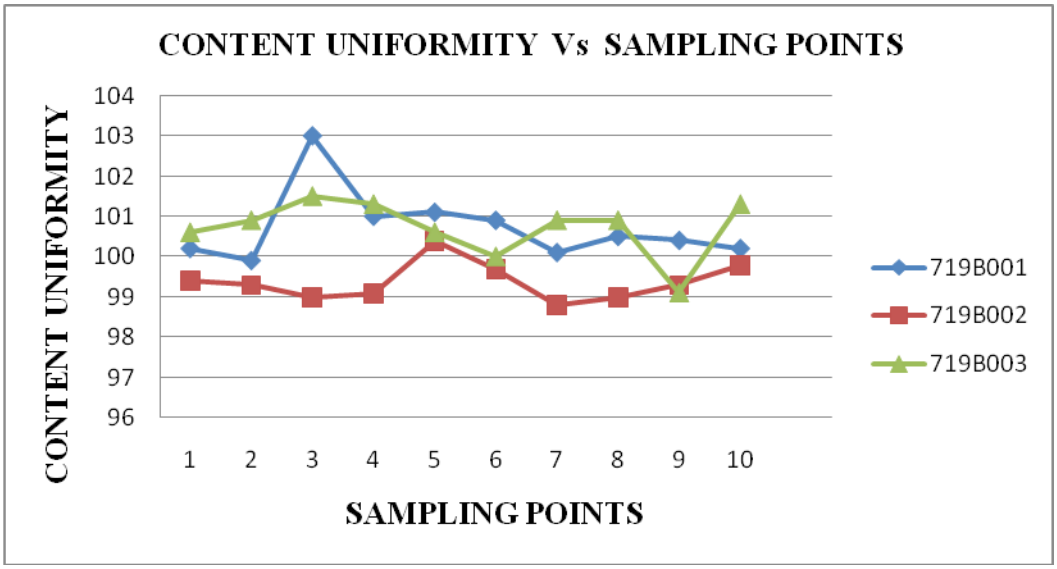


FIG: 16 CONTENT UNIFORMITY FROM SS BIN

7.5 Stage: COMPRESSION

Weight of 10 tablets from each validation batch at three different speeds are given in table 15

Table: 15 Weight of 10 tablets from each batch at minimum, maximum & optimum speeds.

Batch No.	Process variable	Acceptance criteria	Sample No./Description	
			Left	**Right**
719B001	Compression machine at minimum speed (10rpm)	Min:10.29g Target:10.50g Max:10.71g	10.55	10.53
719B002			10.79-10.54	10.53-10.57
719B003			10.52-10.53	10.52-10.54
719B001	Compression machine at maximum speed (18rpm)		10.50-10.51	10.49-10.52
719B002			10.50-10.53	10.50-10.52
719B003			10.54	10.53
719B001	Compression machine at optimum speed (15rpm) First half stage		10.49-10.59	10.51-10.62
719B002			10.50-10.60	10.49-10.60
719B003			10.49-10.54	10.52-10.54
719B001	Compression machine at optimum speed (15rpm) second half stage		10.52-10.54	10.50-10.52
719B002			10.51-10.56	10.49-10.55
719B003			10.49-10.54	10.49-10.54

Stage: COMPRESSION

Disintegration time of sampled tablets from each validation batch at three different speeds are given in table 16

Table: 16 Disintegration time of tablets from each batch at minimum, maximum & optimum speeds

Batch No.	Process variable	Acceptance criteria	Sample No./Description	
			Left	**Right**
719B001	Compression machine at minimum speed (10rpm)	NMT 15 minutes	06 min 15 sec	06 min 20 sec
719B002			06 min 05 sec	06 min 07 sec
719B003			06 min 10 sec	06 min 08 sec
719B001	Compression machine at maximum speed (18rpm)		06 min 21 sec	06 min 18 sec
719B002			06 min 05 sec	06 min 10 sec
719B003			06 min 32 sec	06 min 22 sec
719B001	Compression machine at optimum speed (15rpm) First half stage		06 min 22 sec	06 min 21 sec
719B002			06 min 05 sec	06 min 10 sec
719B003			06 min 18 sec	06 min 11 sec
719B001	Compression machine at optimum speed (15rpm) second half stage		06 min 25 sec	06 min 19 sec
719B002			06 min 12 sec	06 min 10 sec
719B003			06 min 10 sec	06 min 02 sec

Stage: COMPRESSION

Thickness of sampled tablets from each validation batch at three different speeds are given in table 17

Table: 17 Thickness of tablets from each batch at minimum, maximum & optimum speeds

Batch No.	Process variable	Acceptance criteria	Sample No./Description	
			Left	**Right**
719B001	Compression machine at minimum speed (10rpm)	Min: 6.3 mm Max: 6.9mm	6.6 - 6.8	6.6 - 6.7
719B002			6.5 - 6.8	6.5 - 6.8
719B003			6.6 - 6.7	6.5 - 6.7
719B001	Compression machine at maximum speed (18rpm)		6.5 – 6.7	6.6 – 6.8
719B002			6.5 – 6.7	6.6 – 6.7
719B003			6.5 – 6.7	6.6 – 6.7
719B001	Compression machine at optimum speed (15rpm) First half stage		6.4 – 6.8	6.5 – 6.7
719B002			6.5 – 6.7	6.5 – 6.7
719B003			6.5 – 6.8	6.5 – 6.7
719B001	Compression machine at optimum speed (15rpm) second half stage		6.5 – 6.7	6.5 – 6.7
719B002			6.5 – 6.6	6.5 – 6.6
719B003			6.5 – 6.7	6.5 – 6.6

Stage: COMPRESSION

Weight variation of sampled tablets from each validation batch at three different speeds are given in table 18

Table: 18 Weight variation of tablets from each batch at minimum, maximum & optimum speeds

Batch No.		Acceptance criteria	Sample No./Description

	Process variable		**Left**	**Right**
719B001	Compression machine at minimum speed (10rpm)	Min:998mg Target: 1050mg Max: 1102 mg	1032 - 1073	1034 – 1071
719B002			1036 - 1064	1033 - 1066
719B003			1035 - 1077	1035 - 1077
719B001	Compression machine at maximum speed(18 rpm)		1029 - 1078	1028 - 1064
719B002			1024 - 1063	1037 - 1069
719B003			1041 - 1042	1037 - 1064
719B001	Compression machine at optimum speed (15rpm) First half stage		1030 - 1075	1031 - 1075
719B002			1034 - 1072	1035 - 1068
719B003			1035 - 1081	1041 - 1068
719B001	Compression machine at optimum speed (15rpm) second half stage		1032 - 1081	1035 - 1072
719B002			1046 - 1048	1035 - 1067
719B003			1037 - 1067	1034 - 1078

Stage: COMPRESSION

Hardness of sampled tablets from each validation batch at three different speeds are given in table 19

Table: 19 Hardness of tablets from each batch at minimum, maximum & optimum speeds

Batch No.	Process variable	Acceptance criteria	Sample No./Description	
			Left	**Right**

719B001	Compression machine at minimum speed(10 rpm)	Min:16 kp Max: 25 kp	16 – 23	18 - 25
719B002			18 - 23	17 - 23
719B003			19 - 24	18 - 23
719B001	Compression machine at maximum speed (18rpm)		17 - 24	17 - 24
719B002			17 - 22	17 - 24
719B003			17 - 20	20 - 23
719B001	Compression machine at optimum speed (15rpm) First half stage		17 - 25	19 - 25
719B002			17 - 21	17 - 24
719B003			19 - 24	20 - 24
719B001	Compression machine at optimum speed (15rpm) second half stage		19 – 25	19 - 25
719B002			17 - 23	17 - 25
719B003			20 - 24	18 - 23

Stage: COMPRESSION

Physical inspection of sampled tablets from each validation batch at three different speeds are given in table 20

Table: 20 Physical inspection of tablets from each batch at minimum, maximum & optimum speeds

Batch No.		Acceptance criteria	Sample No./Description

	Process variable		**Left**	**Right**
719B001	Compression machine at minimum speed(10 rpm)	Free from physical defects	complies	complies
719B002			complies	complies
719B003			complies	complies
719B001	Compression machine at maximum speed (18rpm)		complies	complies
719B002			complies	complies
719B003			complies	complies
719B001	Compression machine at optimum speed (15rpm) First half stage		complies	complies
719B002			complies	complies
719B003			complies	complies
719B001	Compression machine at optimum speed (15rpm) second half stage		complies	complies
719B002			complies	complies
719B003			complies	complies

Stage: COMPRESSION

Friability of sampled tablets from each validation batch at three different speeds are given in table 21

Table: 21 Friability of tablets from each batch at minimum, maximum & optimum speeds

Batch No.	Process variable	Acceptance criteria	Sample No./Description	
			Left	**Right**

719B001	Compression machine at minimum speed(10 rpm)	NMT 1%	0.2 – 0.3 %	0.3 %
719B002			0.2 – 0.3 %	0.2 %
719B003			0.2 %	0.2 %
719B001	Compression machine at maximum speed (18rpm)		0.3 %	0.2 – 0.3 %
719B002			0.2 – 0.3 %	0.2 %
719B003			0.2 %	0.2 %
719B001	Compression machine at optimum speed (15rpm) First half stage		0.2 – 0.3 %	0.2 %
719B002			0.3 %	0.2 – 0.3 %
719B003			0.2 – 0.3 %	0.2 – 0.3 %
719B001	Compression machine at optimum speed (15rpm) second half stage		0.3 %	0.3 %
719B002			0.2 – 0.3 %	0.2 %
719B003			0.3 %	0.3 %

Stage: COMPRESSION

Dissolution of pooled sample of tablets from each validation batch at three different speeds are given in table 22 and sown graphically in fig 20.

Table: 22 Dissolution of tablets from each batch at minimum, maximum & optimum speeds

Test	Process variable	Acceptance criteria	Sample description	Batch no.		
				719B001	**719B002**	**719B003**

Dissolution	Compression machine at minimum speed(10 rpm)	NLT 80% of the labeled amount of anti convulsant drug dissolved in 15 minutes	Pooled sample	96% 97% 100% 99% 101% 98%	101% 98% 99% 100% 95% 101%	102% 102% 102% 101% 102% 102%
	Compression machine at maximum speed (18rpm)			92% 97% 100% 96% 98% 97%	101% 99% 100% 99% 100% 100%	98% 98% 100% 100% 98% 100%
	Compression machine at optimum speed (15rpm) First half stage			96% 97% 98% 100% 100% 102%	100% 100% 97% 99% 99% 100%	99% 99% 97% 98% 94% 97%
	Compression machine at optimum speed (15rpm) second half stage			101% 98% 92% 100% 100% 94%	100% 99% 100% 101% 99% 100%	100% 101% 98% 99% 97% 99%

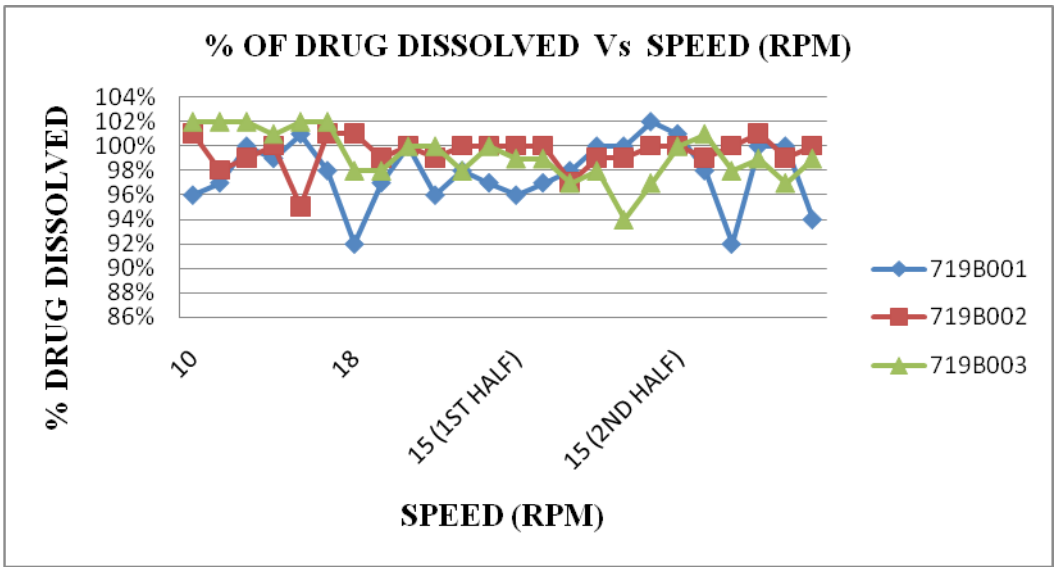


Fig: 20 DISSOLUTION AT DIFFERENT SPEEDS

Stage: COMPRESSION

Content uniformity of pooled sample of tablets from each validation batch at three different speeds are given in table 23 & represented graphically in fig 21.

Table: 23 Content uniformity of tablets from each batch at minimum, maximum & optimum speeds

Test	Process variable	Acceptance criteria	Sample description	Batch no.		
				719B001	**719B002**	**719B003**
Uniformity of dosage units by content uniformity	Compression machine at minimum speed(10 rpm)	Acceptance value should be < L1% (15.0)	Pooled sample	0.7	1.5	1.7
	Compression machine at maximum speed (18rpm)			0.7	1	1.7
	Compression machine at optimum speed (15rpm) First half stage			0.8	1.5	1.4
	Compression machine at optimum speed (15rpm) second half stage			0.8	1.2	1.5

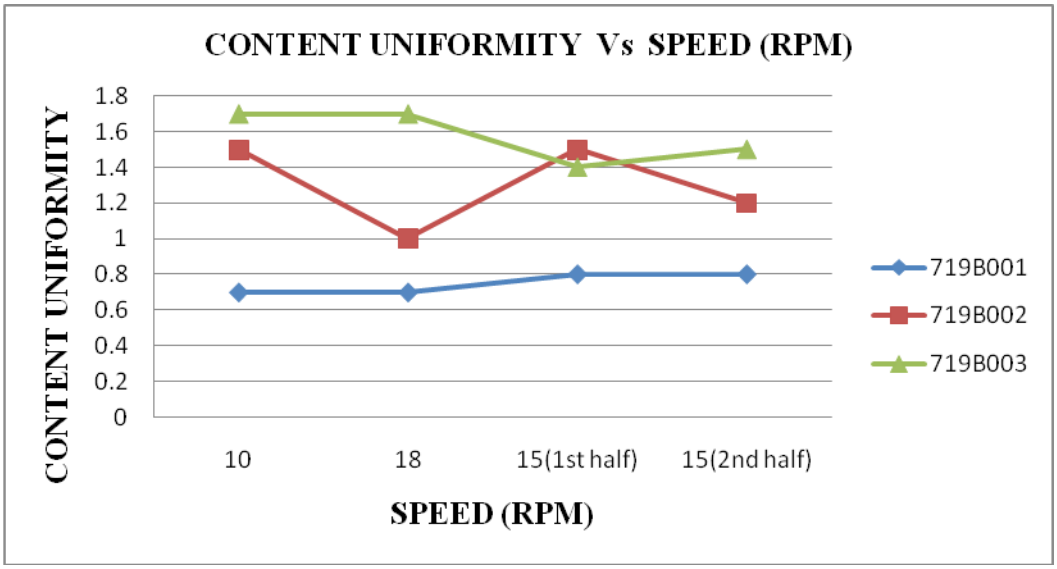


Fig: 21 UNIFORMITY OF DOSAGE UNITS BY CONTENT UNIFORMITY AT DIFFERENT SPEEDS

7.6 Stage: COATING

Dissolution profile of pooled sample of tablets from each validation batch at different time intervals are given in table 24 & shown graphically in fig 22.

Table: 24 Dissolution profile on 12 tablets

Test	Process variable	Acceptance criteria	Sample No./description	Batch No.		
				719B001	**719B002**	**719B003**
Dissolution profile on 12 tablets	coating	For reference purpose	**05 minutes**			
			Avg % of drug dissolved	22.7	32.6	29.7
			% RSD	31.9	24.5	22.3
			10 minutes			
			Avg % of drug dissolved	64.0	72.9	72.2
			% RSD	16.3	12.0	14.1
			15 minutes			
			Avg % of drug dissolved	90.3	94.7	94.4
			% RSD	7.5	5.4	6.1
			30 minutes			
			Avg % of drug dissolved	101.4	102.9	103.0
			% RSD	0.9	0.5	1.2

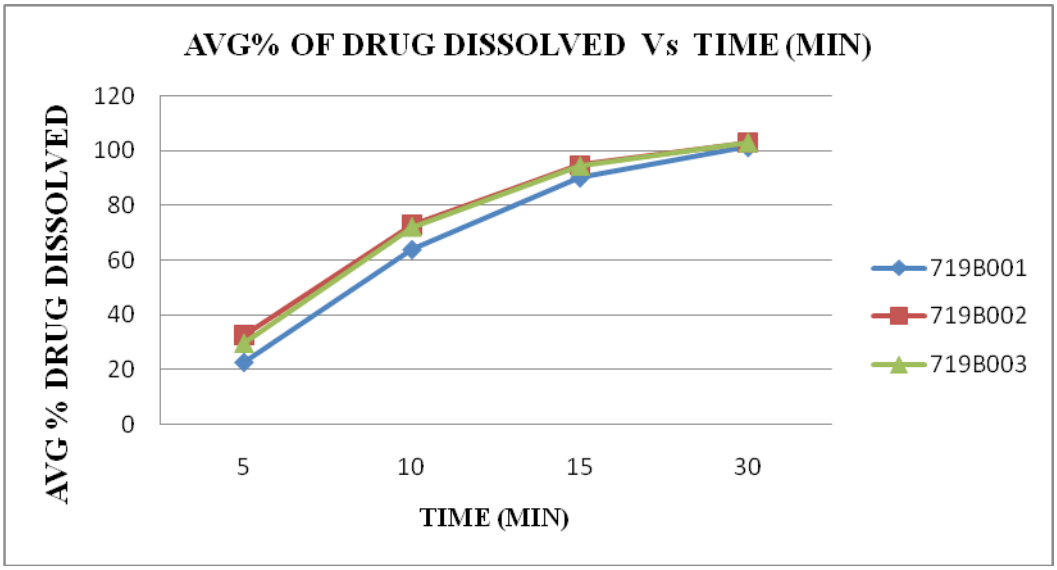


Fig: 22 DISSOLUTION PROFILE ON 12 TABLETS

Stage: COATING

Results of finished product testing of pooled sample of tablets are tabulated in table 25

Table: 25 Finished product testing

Test	Specifications	Batch No.		
		719B001	**719B002**	**719B003**
Description	Blue coloured film coated tablets	Blue coloured film coated tablets	Blue coloured film coated tablets	Blue coloured film coated tablets
Identification a) By HPLC	The retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation, as obtained in the assay	complies	complies	complies
b) By IR	The IR spectrum of sample should match with that of standard	complies	complies	complies
c) By chiral HPLC	The retention time of the major peak should correspond to the retention time of anti convulsant drug peak obtained in the chromatogram of standard solution	complies	complies	complies

Table: 25 Finished product testing (contd…)

Test	Specifications	Batch No.		
		719B001	**719B002**	**719B003**
Water (%W/W) by KF	NMT 3.0	2.3	2.5	2.1
AVG weight (mg)	1076.3±3%	1080.5	1079.2	1075.7
Uniformity of dosage units by weight variation	Acceptance value should be less than or equal to L1%(15.0)	2.0	1.6	0.6
Dissolution	NLT 80% (Q) of the labeled amount of anti convulsant tablet is dissolved in 15 minutes	100% 94% 102% 102% 99% 96%	102% 102% 99% 95% 100% 93%	102% 100% 92% 99% 94% 99%

Dissolution of finished product is represented graphically in fig 23.

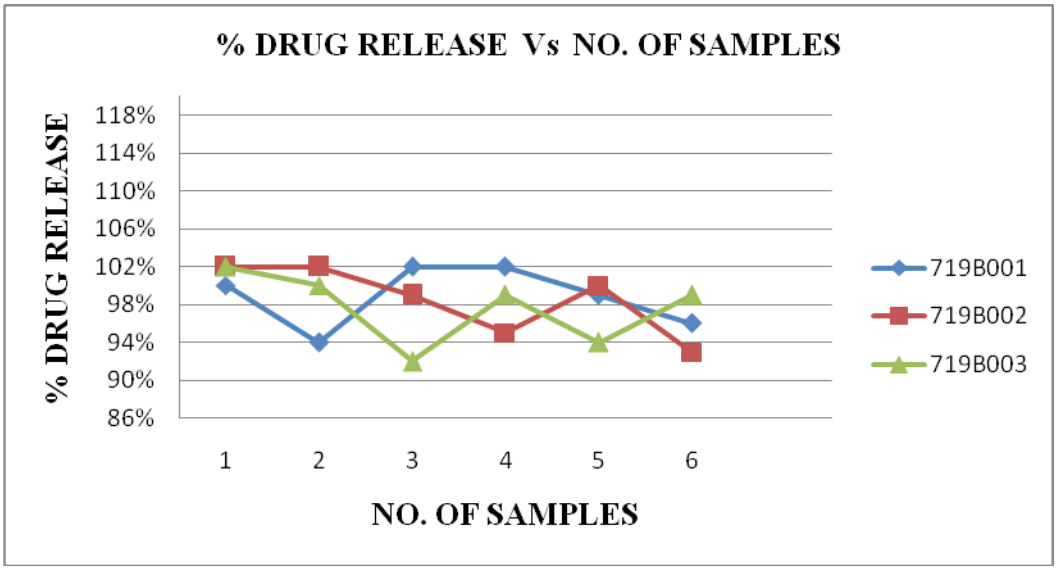


Fig: 23 DISSOLUTION (FINISHED PRODUCT)

Table: 25 Finished product testing (contd…)

Test	Specifications	Batch No.		
		719B001	**719B002**	**719B003**
Assay	Anti convulsant tablets	101.3%	100.6%	100.4%

	contain the equivalent of NLT 90.0% and NMT 110.0% of the labeled amount of anti convulsant drug			
Related substances (%W/W)	Impurity A: NMT 0.2	<LOQ(LOQ= 0.008)	<LOQ(LOQ= 0.008)	<LOQ(LOQ= 0.008)
	Impurity B: NMT 0.05	Not detected	Not detected	Not detected
	Highest unknown impurity: NMT 0.1	0.01%	0.01%	0.01%
	Total impurities: NMT0.5	0.01%	0.02%	0.01%

7.7 Stage: PACKING

Results of packing operations for 120's count are given table 26

Table: 26 Results of packing

Process stage	Test	Acceptance criteria	Batch No.		
			719B001	**719B002**	**719B003**

Tablet counting & filling	Fill count at Min. speed 20 containers/minute	Shall fill 120's count per each bottle at each speed	complies	complies	complies
	Fill count at Max. speed 40 containers/minute		complies	complies	complies
	Fill count at optimum speed 30 containers/minute		complies	complies	complies
Induction sealing	Visual inspection foe seal integrity	Sealing shall be intact	complies	complies	complies
Labeling	Performance of labeling at Min. speed 20 containers/minute	Shall be free from defects	complies	complies	complies
	Performance of labeling at Max. speed 40 containers/minute		complies	complies	complies
	Performance of labeling at optimum speed 30 containers/minute		complies	complies	complies

8.SUMMARY AND CONCLUSION

In the present work, anti convulsant tablets were prepared by direct compression method. All the tablets were subjected to weight variation, drug content uniformity, and hardness, and friability, wetting time, dissolution, drug excipients interaction and short-term stability studies.

Based on the above study following conclusions can be drawn :

- Tablets prepared by direct compression method were found to be good without any chipping, capping and sticking.
- The hardness of the prepared tablets was found to be in the range of 3.2 to 4.1kg/ cm^2.
- The friability values were found to be in the range of 0.41 to 0.49%.
- Disintegration time was found to be in the range of 84sec to 131sec.

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